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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/823,181	03/30/2001	Jingyue Ju	0575/62948/JPW/ADM/BJA	9161

7590 06/14/2004

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 06/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/823,181	JU ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01/07/04, 3/22/04, and 4/27/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *74-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/22/04 & 4/27/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Workgroup 1630, Art Unit 1634, and has been docketed to Primary Examiner Bradley L. Sisson.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 07 January 2004 has been entered.

Specification

3. The specification is objected to as documents have been improperly incorporated by reference. In particular, the specification states

> Throughout this application, various publications are referenced in parentheses by author and year. Full citations for these references may be found at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application to more fully describe the state of the art to which this invention pertains.

Such omnibus language fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited documents. As set forth in *Advanced Display Systems Inc. v. Kent State University* (Fed. Cir. 2000) 54 USPQ2d at 1679:

> Incorporation by reference provides a method for integrating material from various documents into a host document--a patent or printed publication in an anticipation determination--by citing such material in a manner that makes it clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USQP 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). **To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents.** *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-02, 170 USPQ 213, 216-17 (CPA 1971) (reasoning that a rejection or anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference); *National Latex Prods. Co. v. Sun Rubber Co.*, 274 F.2d 224, 230, 123 USPQ 279, 283 (6th Cir. 1959) (requiring a specific reference to material in an earlier application in order to have that material considered a part of a later application); *cf. Lund*, 376 F.2d at 989, 13 USPQ at 631 (holding that **a one sentence reference to an abandoned application is not sufficient to incorporate from the abandoned application into a new application**). (Emphasis added.)

Accordingly, the cited documents are not considered to have been properly incorporated by reference and as such, have not been considered with any effect towards their fulfilling, either in part or in whole, the enablement, written description, or best mode requirements of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision in *University of Rochester v. G.D. Searle & Co.* 68 USPQ2D 1424 (Fed. Cir. 2004) at 1428:

> To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Vas-Cath, 935 F.3d at 1563; see also Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997) (patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention"); In re Gosteli, 872 F.2d 1008, 1012 [10 USPQ2d 1614] (Fed. Cir. 1989) ("the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written-description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572.

6. For convenience, claim 74, the only independent claim currently pending, is reproduced below.

74. (Amended) A method for sequencing DNA which comprises:

(a) treating the DNA with a mixture comprising an oligonucleotide primer, a DNA polymerase, four different deoxynucleotides, and four different labeled dideoxynucleotides, under conditions permitting a deoxynucleotide or a labeled dideoxynucleotide or both to be incorporated into a DNA sequencing fragment, wherein each different deoxynucleotide and each different labeled dideoxynucleotide is complementary to one of the four nuclectides present in the DNA, wherein each labeled dideoxynucleotide comprises a chemical moiety attached via a linker to the dideoxynucleotide; and wherein each of the four different labeled dideoxynucleotides has a molecular weight which can be distinguished from the molecular weight of the other three labeled dideoxynucleotides using mass spectrometry;

(b) generating a plurality of DNA sequencing fragments having different lengths that are terminated with the labeled dideoxynucleotides so as to generate a plurality of different labeled DNA sequencing fragments, wherein each DNA sequencing fragment has a 3′ end and the chemical moiety is attached via the linker to the 3′ end of the DNA sequencing fragment;

(c) contacting the labeled DNA sequencing fragments with a surface coated with a compound that specifically interacts with the chemical moiety attached via the linker to the 3′ end of the DNA sequencing fragments, thereby capturing the labeled DNA sequencing fragments on the surface, wherein the contacting is performed in a system comprising (i) a channel whose surface is coated with a compound that specifically interacts

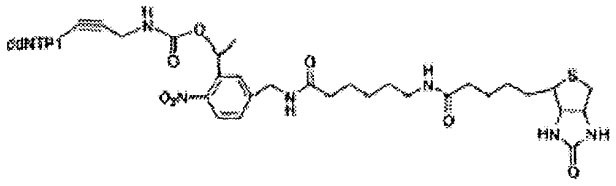
with the chemical moiety, wherein the channel comprises a plurality of ends, (ii) a plurality of wells each suitable for holding a sample, (iii) a connection between each end of the channel and a well, and (iv) a means for moving the sample through the channel between wells;

(d) washing the surface to remove non-bound components;

(e) treating the labeled DNA sequencing fragments so as to release the labeled DNA sequencing fragments from the surface; and

(f) determining the difference in molecular weight between different labeled DNA sequencing fragments which are represented as adjacent peaks on a mass spectra of the labeled DNA sequencing fragments produced using mass spectrometry, so as to sequence the DNA;

wherein either (i) the labeled dideoxynucleotides are biotinylated dideoxynucleotides selected from the group consisting of



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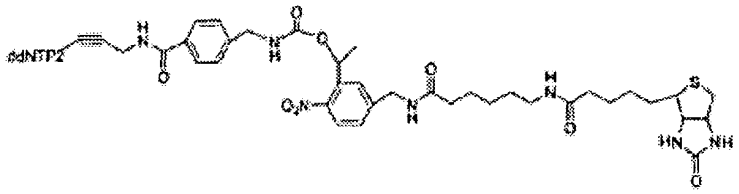

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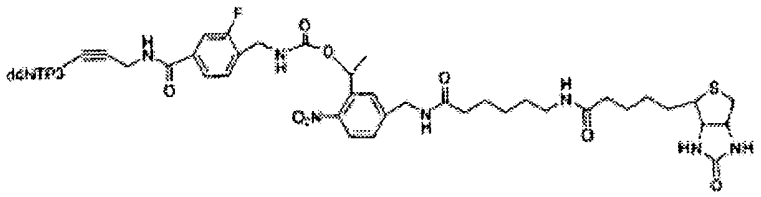

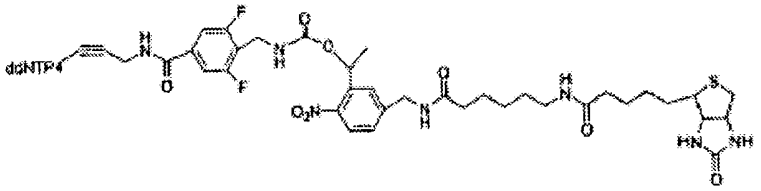

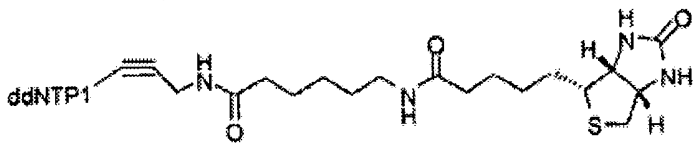

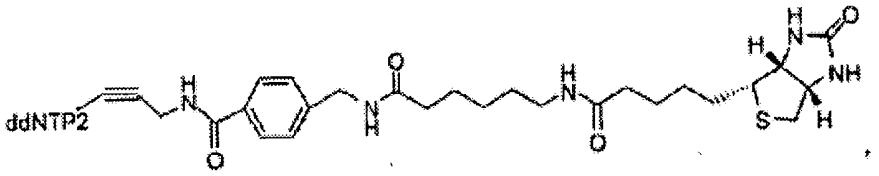

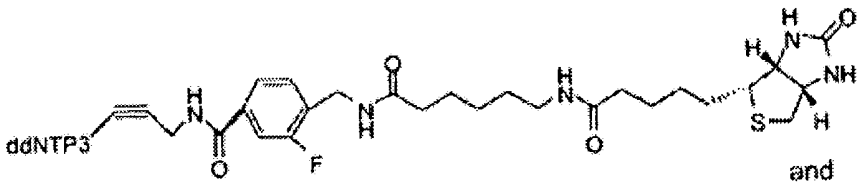

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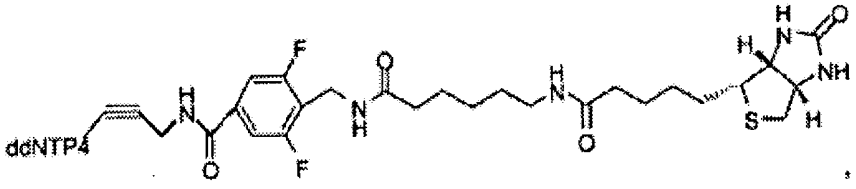
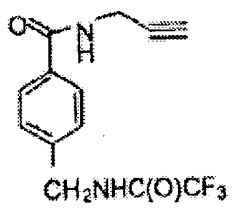
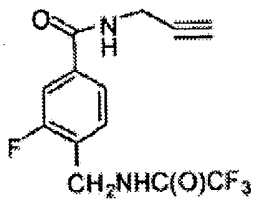


where ddNTP1, ddNTP2, ddNTP3, and ddNTP4 represent four different dideoxynucleotides; or

(ii) the linker is selected from the group consisting of





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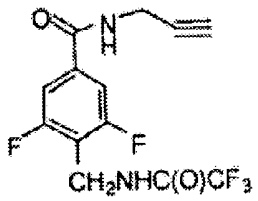

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It is noted that the original application was filed with claims 1-58, that claims 1, 4-5, 7-8, 11-12, 14-15, and 59-73 were canceled and new claims 74-92 added via the amendment of 09 September 2002. The current version of claim 74 was entered via the amendment of 13 January 2003. At page 15 of the response of 09 September 2002, applicant states:

Applicants maintain that new claims 74-92 raise no issue of new matter and are fully supported by the specification as filed. Support for new claim 74 may be found inter alia in the specification, as originally-filed, on page 15, line 10 through page 16, line 32; page 18, line 27 through page 19, line 9; page 20, lines 1-10; page 22, lines 1-10; page 36, line 1 through page 37, line 32; page 12, lines 1-30; and Figures 1-3. Support for

7. For purposes of examination, claim 74 has been interpreted s encompassing a system whose surface has been "coated with a compound" where the coating is by covalent or non-covalent binding means.

8. Said claim has also been interpreted as encompassing a system where a plurality of wells are in series for each channel, and that the sample is immobilized to the coated surface of the channels by a single passage of the sample through said channels and wells.

9. The claimed method has also been interpreted as encompassing the use of coated channels that are open/exposed on one side as well as channels that are entirely closed except for the ends.

10. The claimed method has been interpreted as encompassing the release of the immobilized DNA sequencing fragments by virtually any means, which include but are not limited to, heating, application of light, application of one or any combination of chemicals.

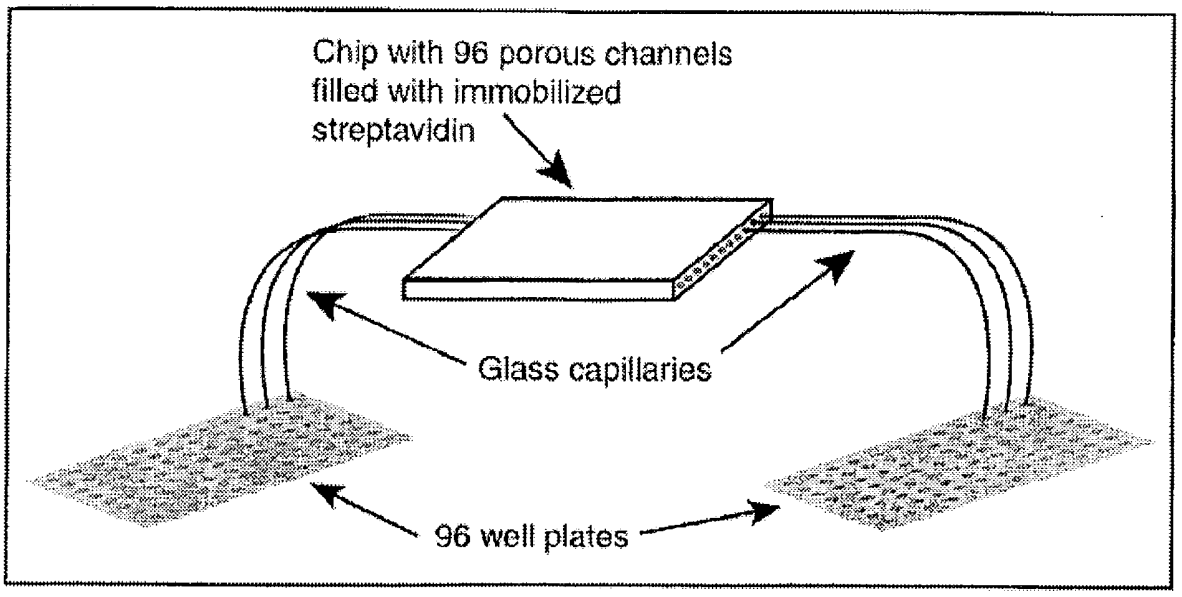
11. Said claim has been interpreted as encompassing determining the difference in molecular weight between different labeled DNA sequencing fragments via mass spectrometry, where the DNA sequencing fragments have not been further manipulated or modified since passage through the channel(s) and well(s). To that end, the claimed method fairly encompasses

practicing a method where the samples are not free from alkaline or alkaline-earth salts, or any other contaminant. The instant specification, however, cautions artisans thusly:

> However, in order to obtain accurate measure of the mass of the sequencing DNA fragments, the samples must be free from alkaline and alkaline-earth salts. Samples must be desalted and free from contaminants before the MS analysis.

A review of the specification, including the passages cited by applicant, fails to find an adequate written description of where mass spectrometry is performed on the DNA sequencing fragments where the sample contains any of the above-noted contaminants.

12. As noted above, the claimed method has been interpreted as comprising a plurality of wells connected via a channel, where the channel and wells are within a chip. A review of the disclosure, however, fails to find an adequate written description of such a device. Rather, the specification has been found to provide a description via Fig. 12, of two 96-well plates that are connected via glass capillary tubes to corresponding single channels in a chip.



It is noted with particularity that the device described lacks any means for applying pressure such that any one, much less 96 different samples could be passed through the coated channels in one direction, much less back-and-forth, thereby permitting/enabling the binding of the DNA sequencing fragments.

13. As noted above, the claimed method has been interpreted as requiring but a single pass of the sample through the channels, however, page 48, lines 26-29, describes a method requiring pressure to be applied in reverse in order to drive "the sample through the channel multiple times," thereby ensuring a high efficiency solid phase capture. Assuming *arguendo*, that the specification does suggest performing but a single pass of the sample through the channel, the specification has not been found to provide an adequate written description of how adequate quantities of DNA sequencing fragments are to be bound, and subsequently released and then analyzed such that the nucleotide sequence could be accurately and reproducibly determined, especially when the quantity of starting material is severely limited.

14. The claimed method has also been interpreted as encompassing the simultaneous sequencing of multiple DNA sequencing fragments in a common channel. To perform such a maneuver would present situations where multiple signals would be generated at the same time, yet would correspond to the different templates. The use of knowingly different DNA fragments will cause situations where the nucleotide sequence is anything but clearly resolvable. The specification has not been found to provide an adequate written description of how this issue is to be overcome.

15. The claimed method fairly encompasses the use of mass spectrometry in the analysis of the DNA fragments. The use of lasers in performing mass spectrometry is recognized in the art

as causing significant problems in sequencing. In support of this position attention is directed to US Patent Application Publication 2002016842A1 teaches at paragraph 13:

> A problem encountered with MALDI of simplex DNA is breakage. Initial trials with short homogenous simplexes revealed severe fragmentation problems ("Matrix-assisted laser-desorption mass spectrometry of DNA using an infrared free-electron laser," Haugland, R. F. et al.; Proc. SPIE-Int. Soc. Opt. Eng., 1854 (FEL), 1993). Two distinct molecules of lower mass are split off by a break in the deoxyribose-phosphodiester backbone of single stranded DNA. Even for a homogenous population of single stranded DNAs, the resultant fragments have a broad range of lower masses. For projected heterogeneous single stranded Pop as inputs for sequencing, lower mass members will be within the fragmentation background and thus harder to recognize.

The specification of the subject application has not been found to provide an adequate written description as to how art-recognized issues are to be overcome.

16. In view of the breadth of the claims, the limited written description provided, the specification has not been found to provide an adequate written description of the invention. Similarly, the specification has not been found to reasonably suggest that applicant was in possession of the invention at the time of filing. Therefore, and in the absence of convincing evidence to the contrary, claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

17. As presented above, the specification has not been found to provide an adequate written description of the invention to where the specification does not reasonably suggest that applicant did not possess the entire invention at the time of filing. It is well settled that one cannot enable that which they do not yet possess.

18. Further, the records clearly shows that the claimed method fairly encompasses embodiments where art-recognized issues of enablement would be encountered, yet the specification is effectively silent as to how they are to be overcome sans the skilled artisan resort to undue experimentation.

19. Therefore, and in the absence of convincing evidence to the contrary, claims 74-92 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
07 June 2004